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(54) Substituted thiazolidinedione derivatives

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Thiazolidinediones substituées

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(73) Proprietor: BEECHAM GROUP PLC
Brentford, Middlesex TW8 9EP (GB)

(72) Inventor: Hindley, Richard Mark
Beecham Pharmaceuticals
Epsom Surrey, KT18 5XQ (GB)

(74) Representative: Rutter, Keith, Dr. et al
SmithKline Beecham plc
Corporate Intellectual Property,
Two New Horizons Court
Brentford, Middlesex TW8 9EP (GB)

(56) References cited:
EP-A- 0 008 203

- CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 30, no. 10, October 1982, pages 3580-3600, Tokyo, JP; T. SOHDA et al.: "Studies on antidiabetic agents. II.1) Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives"
- Bioorganic & Medicinal Chemistry Letters 1994; Vol. 4, No. 9, 1181-1184
- Chem. Pharm. Bull. 1991; Vol. 39, No. 6, 1440-1445

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EP 0 306 228 B1

Description

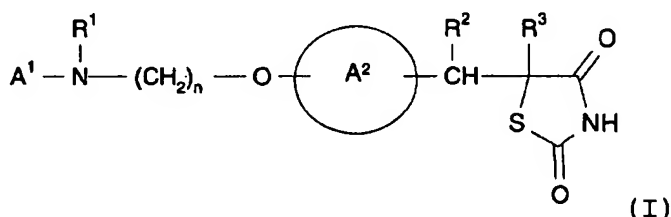
[0001] This invention relates to a certain substituted thiazolidinedione derivative, to pharmaceutical compositions containing such a compound and to the use of such a compound and compositions in medicine.

[0002] European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and 0208420 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580-3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

[0003] It has now surprisingly been discovered that a certain novel substituted-thiazolidinedione derivative shows improved blood-glucose lowering activity and is therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

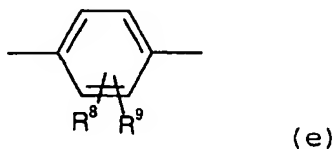
[0004] This compound is also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

[0005] Accordingly, the present invention provides a compound of formula (I):



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

- A¹ represents a 2-pyridyl group;
- R¹ represents a methyl group;
- R² and R³ each represent hydrogen;
- A² represents a moiety of formula (e):



wherein R⁸ and R⁹ each represent hydrogen; and n represents an integer 2.

[0006] The compound of formula (I) is 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

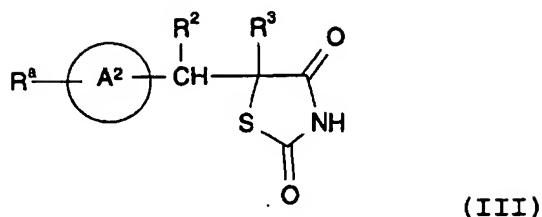
[0007] As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

[0008] Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety.

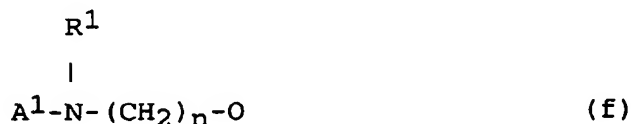
[0009] Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts.

[0010] Suitable pharmaceutically acceptable solvates include hydrates.

[0011] In a further aspect there is also provided a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises reacting a compound of formula (III):



wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (f):



wherein R^1 , A^1 , and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

[0012] Suitably, R^a represents $R^1\text{HN}-(\text{CH}_2)_n\text{-O-}$ wherein R^1 and n are as defined in relation to formula (I).

[0013] Suitably, when R^a is $R^1\text{HN}-(\text{CH}_2)_n\text{-O-}$, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (IV):

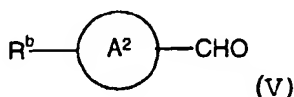


wherein A^1 is as defined in relation to formula (I) and R^x represents a leaving group.

[0014] A suitable leaving group R^x includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

[0015] The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the above-mentioned reaction between a compound of formula (III) wherein R^a represents $R^1\text{HN}-(\text{CH}_2)_n\text{-O-}$ and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0 and 60°C.

[0016] A compound of formula (III) may be prepared from a compound of formula (V):



wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a , or a moiety convertible to a moiety R^a ; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, into a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

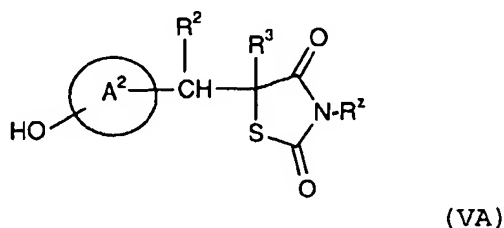
(ii) converting a moiety R^b to a moiety R^a .

[0017] The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out

under conditions suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

[0018] When R^a represents $R^1HN-(CH_2)_n-O-$, a suitable value for R^b is a hydroxyl group.

[0019] The moiety R^b may be converted to the moiety R^a by any suitable means, for example when R^b represents a hydroxyl group and R^a represents $R^1HN(CH_2)_n-O-$ the appropriate conversion may be carried out by coupling a compound of formula (VA):



wherein R^2 , R^3 and A^2 are as defined in relation to formula (I) and R^2 is hydrogen or a nitrogen protecting group, with a compound of formula (VI):



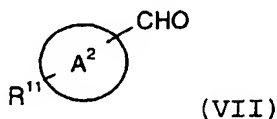
wherein R^1 and n are as defined in relation to formula (I) and R^x is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) removing any nitrogen protecting group.

[0020] A suitable coupling agent for the coupling reaction between the compound of formula (VA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

[0021] One example of the preparation of a compound of formula (VA) is that wherein a compound falling within formula (V) of particular formula (VII):



wherein A^2 is as defined in relation to formula (I), and R^{11} represents a hydroxyl group or a protected hydroxyl group, is reacted with 2,4-thiazolidinedione; and thereafter if required removing any protecting group.

[0022] Preferably, R^{11} represents a benzyloxy group.

[0023] Suitable conditions for the reaction between a compound of formula (VII) and 2,4-thiazolidinedione are those defined above in relation to the reaction between the compounds of formula (V) and 2,4-thiazolidinedione.

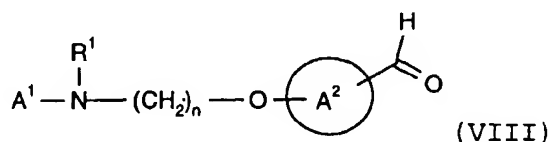
[0024] The compounds of formula (IV), (VI) and (VII) are either known compounds or are prepared using methods analogous to those used to prepare known compounds.

[0025] Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art.

Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a suitable hydroxyl protecting group is a benzyl group.

[0026] The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example when R¹¹ represents a benzyloxy group such group may be prepared by treatment of the appropriate compound of formula (VII), wherein R¹¹ is a hydroxyl group with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide.

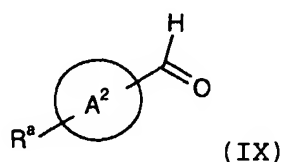
[0027] A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula (VIII):



wherein R¹, A¹, A², and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; reducing the compound so formed and thereafter if required, preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

[0028] The reaction between a compound of formula (VIII) and 2,4-thiazolidinedione may suitably be carried out under analogous conditions to those used in the reaction between a compound of formula (V) and 2,4-thiazolidinedione.

[0029] A compound of formula (VIII) may be prepared by reacting a compound of formula (IX):



wherein A² is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to the above defined moiety (f).

[0030] Suitable values for R^a include those described above in relation to the compound of formula (III). Thus R^a may represent R¹HN-(CH₂)_n-O-, as defined above, and hence the appropriate compound of formula (IX) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (VIII).

[0031] Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

[0032] Preferably, for the compound of formula (IX), R^a represents a leaving group, especially a fluorine atom. When R^a represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (X):

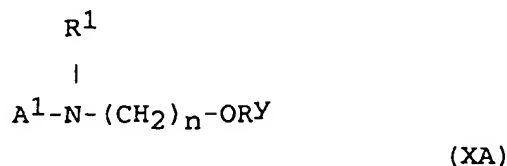


wherein R¹, A¹, and n are as defined in relation to formula (I).

[0033] The reaction between the compounds of formulae (IX) and (X) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for example in the range of between 100 to 150°C, suitably in the presence of a base such as sodium hydride or potassium carbonate.

[0034] In the compound of formula (IX) R^a may also represent a hydroxyl group.

[0035] When R^a, in the compound of formula (IX), represents a hydroxyl group a particularly appropriate reagent is a compound of the abovedefined formula (X) or a compound of formula (XA):



wherein A¹, R¹ and n are as defined in relation to formula (X) and R^Y represents a tosylate or mesylate group.

[0036] The reaction between the compound of formula (IX) wherein R^a is a hydroxyl group and the reagent of the abovedefined formula (X) may suitably be carried out in an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, and preferably in the presence of a coupling agent such as that provided by triphenylphosphine and diethylazodicarboxylate.

[0037] The reaction between the compound of formula (IX), wherein R^a is a hydroxyl group, and the reagent of the abovedefined formula (XA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50°C to 120°C and preferably in the presence of a base, such as sodium hydride.

[0038] The compound of formula (XA) may be prepared from the corresponding compound of formula (X) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

[0039] The compounds of formula (IX) are known compounds or compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds.

[0040] The reagent of formula (X) may be prepared by reacting a compound of the hereinabove defined formula (IV), with a compound of the hereinbefore defined formula (VI) and thereafter if required removing any nitrogen protecting group using the appropriate conventional conditions.

[0041] The reaction between the compounds of formula (IV) and (VI) may be carried out under any suitable conditions, such as in solvent, for example in an aprotic solvent such as tetrahydrofuran, at a low to medium temperature, for example a temperature in the range of from 0 to 60°C.

[0042] Favourably when R¹ represents hydrogen the reaction is carried out using the compound of formula (VI) as a solvent at a low to elevated temperature, suitably an elevated temperature such as in the range of between 100 and 170°C.

[0043] The abovementioned reductions of:

(i) a compound of formula (III) wherein R² and R³ together represent a bond to a compound of formula (III) wherein R² and R³ each represent hydrogen, and

(ii) the compound formed by reaction of the compound of formula (VIII) and 2,4-thiazolidinedione,

may be carried out using the appropriate conventional procedure, including catalytic reduction or the use of a metal/solvent reducing system.

[0044] Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature.

[0045] Suitable metal/solvent reducing systems include magnesium in methanol.

[0046] Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

[0047] When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

[0048] When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

[0049] Suitable alkyl groups are C₁₋₁₂ alkyl groups, especially C₁₋₆ alkyl groups e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl groups.

[0050] As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

[0051] The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

[0052] Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

[0053] In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

[0054] As indicated hereinbefore the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

[0055] A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

[0056] Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

[0057] As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

[0058] The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

[0059] Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

[0060] Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

[0061] In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

[0062] Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycolate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

[0063] Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

[0064] Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

[0065] In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

[0066] In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be administered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

[0067] The dosages regimens for the treatment of hypertension, -cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

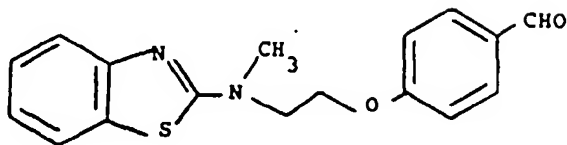
[0068] In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

[0069] The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof; and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

[0070] The following Procedures and Examples illustrate the invention.

Reference Preparation 14-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benzaldehyde

[0071]



[0072] A mixture of 4-fluorobenzaldehyde (1.5g) and 2-[N-methyl-N-(2-benzothiazolyl)amino]ethanol (2.4g) in dimethyl sulphoxide (50ml) containing anhydrous potassium carbonate (2g) was stirred at 100°C for 24 hours. The mixture was cooled to room temperature and added to water (300ml). The aqueous solution was extracted with diethyl ether (2x300ml). The organic extracts were washed with brine (1x300ml), dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as a waxy solid following chromatography on silica-gel in 1% methanol in dichloromethane.

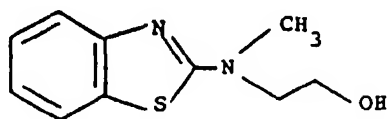
¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t);

6.8-7.8 (8H, complex); 9.8 (1H, s).

Reference Preparation 22-[N-Methyl-N-(2-benzothiazolyl)amino]ethanol

[0073]

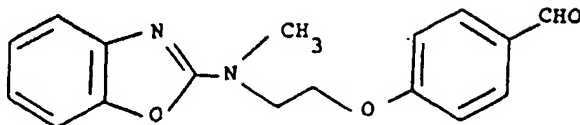


[0074] A mixture of 2-chlorobenzothiazole (8.5g) and 2-methylaminoethanol (20ml) was heated at 120°C under pressure in a sealed, glass lined, stainless steel reaction vessel for 18 hours. After cooling, the oil was added to water (100ml), extracted with dichloromethane (2x100ml), the organic extracts were dried (MgSO₄), filtered and evaporated to dryness. Chromatography of the residual oil on silica-gel in 2½% methanol in dichloromethane gave the title compound which was used in Reference Preparation 1 without further purification.

¹H NMR δ (CDCl₃)3.15 (3H, s); 3.4-4.0 (4H, m); 4.7 (1H, broad s, exchanges with D₂O); 6.8-7.6 (4H, complex).

Reference Preparation 34-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

[0075]



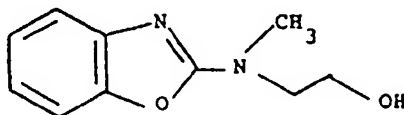
[0076] To a solution of 2-[N-methyl-N-(2-benzoxazolyl) amino]ethanol (9.6g), triphenylphosphine (13.1g) and 4-hydroxybenzaldehyde (6.1g) in dry tetrahydrofuran (150ml) was added dropwise a solution of diethyl azodicarboxylate (9.0g) in dry tetrahydrofuran (30ml), under a blanket of nitrogen with stirring at room temperature. The solution was stirred overnight at room temperature following which the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (300ml), filtered and the ether solution was washed with dilute sodium hydroxide solution (200 ml), saturated brine (200ml), dried (MgSO₄), filtered and the solvent evaporated. The title compound (mp 97-98°C) was obtained after chromatography on silica-gel, eluting with dichloromethane.

¹H NMR δ (CDCl₃)

3.30 (3H, s); 3.85 (2H, t); 4.30 (2H, t) 6.80-7.85 (8H, complex); 9.85 (1H, s).

Reference Preparation 42-[N-Methyl-N-(2-benzoxazolyl)amino]ethanol

[0077]

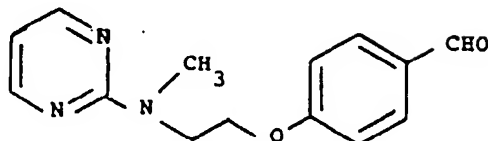


[0078] A solution of 2-chlorobenzoxazole (15.4g) in dry tetrahydrofuran (50ml) was added dropwise to an ice cooled solution of 2-methylaminoethanol (15.0g) in dry tetrahydrofuran (100ml) with stirring and protection from atmospheric moisture. The mixture was stirred at 0°C for 1 hour, allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, the product was dissolved in ethyl acetate (200ml) and washed with brine (2x150ml). The organic layer was dried (MgSO₄), filtered and the solvent evaporated. Chromatography of the residue on silica-gel in dichloromethane gave the title compound (mp 62-3°C) which was used in Reference Preparation 3 without further purification.

¹H NMR δ (CDCl₃)3.12 (3H s); 3.4-4.0 (4H, m); 4.7 (1H, s, exchanges with D₂O); 6.8-7.4 (4H, complex).

Reference Preparation 54-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzaldehyde

[0079]



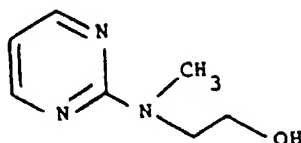
[0080] A mixture of 4-fluorobenzaldehyde (12ml) and 2-[N-methyl-N-(2-pyrimidinyl)amino]ethanol (10.05g) in dry dimethyl sulphoxide (50ml) containing anhydrous potassium carbonate (15g) was stirred at 120°C for 6 hours. The mixture was cooled to room temperature and added to water (200ml). The aqueous solution was extracted with ethyl acetate (2 x 300ml), the organic extracts washed with brine, dried (MgSO₄) and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

3.3 (3H, s); 3.8-4.4 (4H, complex); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

Reference Preparation 62-[N-Methyl-N-(2-pyrimidinyl)amino]ethanol

[0081]

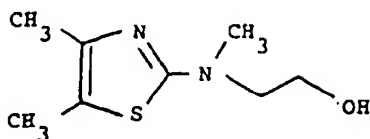


[0082] A mixture of 2-chloropyrimidine (10g) and 2-methylaminoethanol in dry tetrahydrofuran (100ml) was boiled under reflux for 3 hours. The solution was cooled, water (200ml) was added, the mixture extracted with dichloromethane, the organic extracts were dried (MgSO₄), filtered and evaporated to dryness. The residual oil was used in Reference Preparation 5 without further purification.

¹H NMR δ (CDCl₃)3.2 (3H, s); 3.5-3.9 (4H, m); 4.6 (1H, s, exchanges with D₂O); 6.4 (1H, t); 8.2 (2H, d).

Reference Preparation 72-[N-Methyl-N-(2-[4,5-dimethylthiazolyl])amino]ethanol

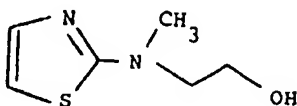
[0083]



[0084] A solution of 2-chloro-4,5-dimethylthiazole (13.2g) and 2-methylaminoethanol (40ml) in pyridine (100ml) was boiled under reflux for 20 hours. After cooling, the oil was added to water (300ml) and extracted with ethyl acetate (3x200ml). The organic extracts were washed with brine (2x200ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound which was used in Reference Preparation 14 without further purification.

¹H NMR δ (CDCl₃)2.15 (3H, s); 2.20 (3H, s); 3.1 (3H, s); 3.4-3.9 (4H, m); 5.25 (1H, broad s, exchanges with D₂O).Reference Preparation 82-[N-Methyl-N-(2-thiazolyl)amino]ethanol

[0085]

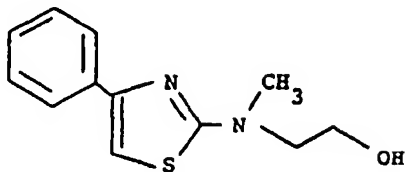


[0086] The title compound was prepared as an oil from 2-bromothiazole (15g) and 2-methylaminoethanol (45ml) by an analogous procedure to that described in Reference Preparation 7

¹H NMR δ (CDCl₃)3.1 (3H, s); 3.4-3.9 (4H, m); 4.8 (1H, broad s, exchanges with D₂O); 6.4 (1H, d); 7.0 (1H, d).

Reference Preparation 92-[N-Methyl-N-(2-(4-phenylthiazolyl))amino]ethanol

[0087]



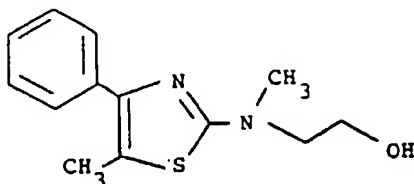
[0088] The title compound was prepared as an oil from 2-chloro-4-phenylthiazole (13.5g) and 2-methylaminoethanol (40ml) by an analogous procedure to that described in Reference Preparation 7.

¹H NMR δ (CDCl₃)

3.15 (3H, s); 3.6-4.0 (4H, m); 4.6 (1H, broad s, exchanges with D₂O); 6.7 (1H, s); 7.2-7.9 (5H, complex).

Reference Preparation 102-[N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol

[0089]



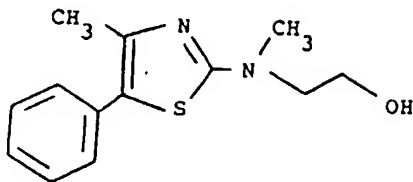
[0090] The title compound was prepared as an oil from 2-chloro-4-phenyl-5-methylthiazole (18.9g) and 2-methylaminoethanol (50ml) by an analogous procedure to that described in Reference Preparation 7.

¹H NMR δ (CDCl₃)

2.38 (3H, s); 3.0 (3H, s); 3.45-3.85 (4H, m); 5.1 (1H, broad s, exchanges with D₂O); 7.1-7.7 (5H, complex).

Reference Preparation 112-[N-Methyl-N-(2-(4-methyl-5-phenylthiazolyl))amino]ethanol

[0091]



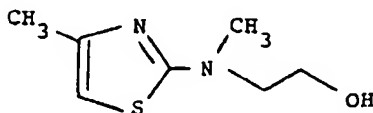
[0092] The title compound was prepared as an oil from 2-chloro-4-methyl-5-phenylthiazole (14.8g) and 2-methylaminoethanol (40ml) by an analogous procedure to that described in Reference Preparation 7.

¹H NMR δ (CDCl₃)

2.35 (3H, s); 3.1 (3H, s); 3.5-4.0 (4H, m); 5.1 (1H, broad s, exchanges with D₂O); 7.1-7.5 (5H, complex).

Reference Preparation 122-[N-Methyl-N-(2-(4-methylthiazolyl))amino]ethanol

[0093]



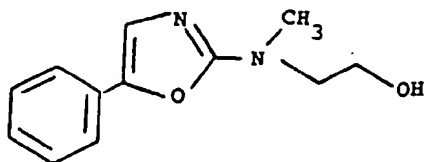
[0094] The title compound was prepared, by an analogous procedure to that described in Reference Preparation 7, and was used in the next stage without further purification.

¹H NMR δ (CDCl₃)

2.25 (3H, s); 3.1 (3H, s); 3.55-3.95 (4H, m); 4.9 (1H, broad s, exchanges with D₂O); 6.1 (1H, s).

Reference Preparation 132-[N-Methyl-N-[2-(5-phenyloxazolyl)]amino]ethanol

[0095]



[0096] A solution of 2-chloro-5-phenyloxazole (8.3g) and 2-methylaminoethanol (30ml) was stirred at 50°C for 10 minutes. After cooling the oil was added to water (250ml) and extracted with ethyl acetate (2x150ml). The organic

extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound (m.p. 73-75°C).

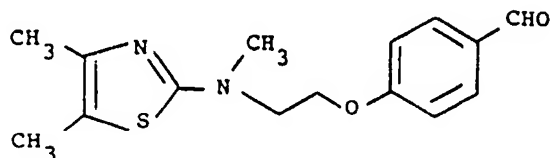
¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.6 (2H, t); 3.85 (2H, t); 3.9 (1H, broad s, exchanges with D₂O); 7.0 (1H, s); 7.2-7.55 (5H, complex).

Reference Preparation 14

4-[2-(N-Methyl-N-(2-(4,5-dimethylthiazolyl)amino)ethoxy)]benzaldehyde

[0097]



[0098] The title compound was prepared from 2-[N-methyl-N-(2-(4,5-dimethylthiazolyl)amino)]ethanol (13.2g) and 4-fluorobenzaldehyde (23.1g) by an analogous procedure to that described in Reference Preparation 5.

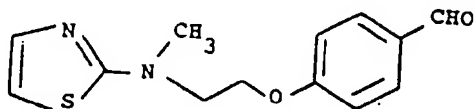
¹H NMR δ (CDCl₃)

2.15 (3H, s); 2.2 (3H, s); 3.18 (3H, s); 3.8 (2H, t); 4.3 (2H, t); 7.0 (2H, d); 7.8 (2H, d); 10.0 (1H, s).

Reference Preparation 15

4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzaldehyde

[0099]



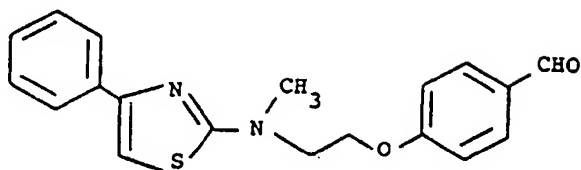
[0100] The title compound was prepared from 2-[N-methyl-N-(2-thiazolyl)amino]ethanol (10.7g) and 4-fluorobenzaldehyde (15.9g) by an analogous procedure to that described in Reference Preparation 5.

¹H NMR δ (CDCl₃)

3.15 (3H, s); 3.9 (2H, t); 4.4 (2H, t); 6.5 (1H, d);
7.0 (2H, d); 7.15 (1H, d); 7.8 (2H, d); 9.9 (1H, s).

Reference Preparation 164-[2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy] benzaldehyde

[0101]



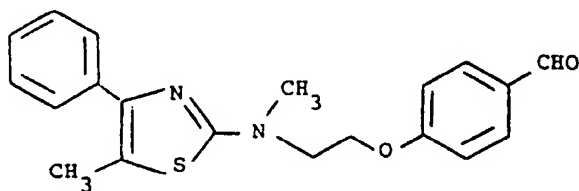
[0102] The title compound was prepared from 2-[N-methyl-N-(2-(4-phenylthiazolyl))amino]ethanol (16.1g) and 4-fluorobenzaldehyde (17.4g) by an analogous procedure to that described in Reference Preparation 5.

¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.95 (2H, t); 4.3 (2H, t); 6.7 (1H, s); 6.95-7.9 (9H, complex); 9.9 (1H, s).

Reference Preparation 174-[2-(N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino) ethoxy]benzaldehyde

[0103]



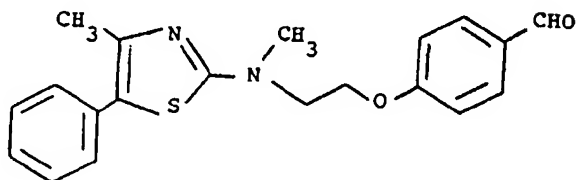
[0104] The title compound was prepared from 2-[N-methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol (13g) and 4-fluorobenzaldehyde (9.8g) by a similar procedure to that described in Reference Preparation 5.

¹H NMR δ (CDCl₃)

2.35 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.85-7.8 (9H, complex); 9.85 (1H, s).

Reference Preparation 184-[2-(N-Methyl-N-(2-(4-methyl-5-phenyl-thiazolyl))amino)ethoxy]benzaldehyde

[0105]



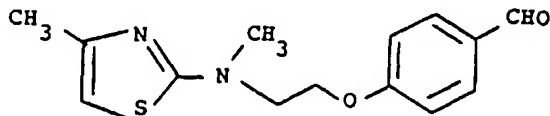
[0106] The title compound was prepared from 2-[N-methyl-N-(2-(4-methyl-5-phenylthiazolyl))amino]ethanol (13g) and 4-fluorobenzaldehyde (13g) by an analogous procedure to that described in Reference Preparation 5.

¹H NMR δ (CDCl₃)

2.36 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.05 (2H, d); 7.2-7.5 (5H, complex); 7.85 (2H, d); 9.95 (1H, s).

Reference Preparation 194-[2-(N-Methyl-N-(2-(4-methylthiazolyl))amino)ethoxy] benzaldehyde

[0107]



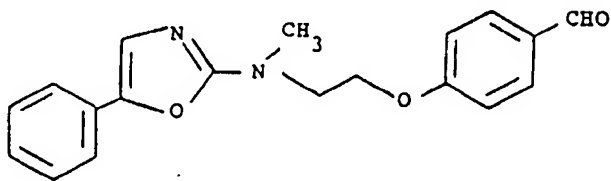
[0108] The title compound was prepared from 2-[N-methyl-N-(2-(4-methylthiazolyl))amino]ethanol (12g) and 4-fluorobenzaldehyde (14.3g) by an analogous procedure to that described in Reference Preparation 5.

¹H NMR δ (CDCl₃)

2.25 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.3 (2H, t); 6.1 (1H, s); 7.05 (2H, d); 7.85 (2H, d); 9.95 (1H, s).

Reference Preparation 204-[2-(N-Methyl-N-(2-(5-phenyloxazolyl))amino)ethoxy] benzaldehyde

[0109]



[0110] The title compound was prepared from 2-[N-methyl-N-(2-(5-phenyloxazolyl))amino]ethanol (9.3g) and 4-fluorobenzaldehyde (7.9g) by an analogous procedure to that described in Reference Preparation 5.

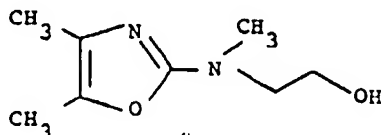
¹H NMR δ (CDCl₃)

3.25 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.95-7.6 (8H, complex); 7.8 (2H, d); 9.9 (1H, s).

Reference Preparation 21

2-[N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino]ethanol.

[0111]



[0112] A solution of 2-chloro-4,5-dimethyloxazole (5g) and 2-methylaminoethanol (15ml) was stirred at 120°C for 40 minutes. After cooling the oil was added to water (200ml) and extracted with dichloromethane (3x200ml). The organic extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness to leave the title compound as a waxy solid, which was used in Reference Preparation 22 without further purification.

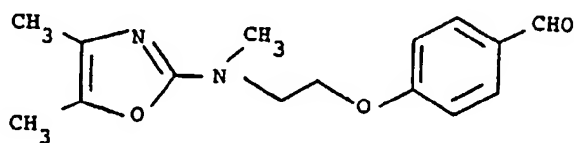
¹H NMR δ (CDCl₃)

1.95 (3H, s); 2.10 (3H, s); 3.05 (3H, s); 3.5 (2H, t); 3.8 (2H, t); 4.4 (1H, broad s, exchanges with D₂O).

Reference Preparation 22

4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino) ethoxy]benzaldehyde

[0113]



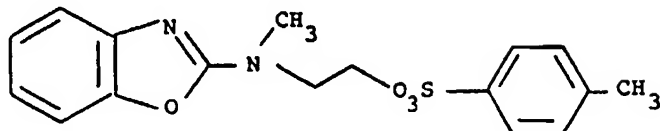
[0114] To a stirred solution of 2-[N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino]ethanol (2.7g) in DMF (60ml), under an atmosphere of nitrogen, was added portionwise sodium hydride (0.7g; 60% dispersion in oil). After the vigorous reaction had subsided, 4-fluorobenzaldehyde (2.9g) was added and the reaction mixture was heated to 80°C for 16 hours. After cooling, the mixture was added to water (400ml). The aqueous solution was extracted with diethyl ether (3x250ml). The organic extracts were washed with brine (2x100ml), dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as an oil following chromatography of the residue on silica-gel in 1% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

1.95 (3H, s); 2.15 (3H, s); 3.15 (3H, s); 3.8 (2H, t); 4.25 (2H, t); 7.0 (2H, d); 7.9 (2H, d); 10.0 (1H, s).

Reference Preparation 232-(N-(2-Benzoxazolyl)-N-methylamino)ethanol 4-toluenesulphonyl ester

[0115]



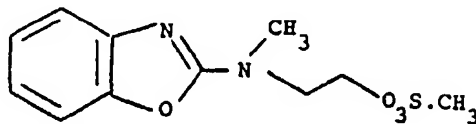
[0116] 4-Toluenesulphonyl chloride (19.0g) was added portionwise to a solution of N-(2-benzoxazolyl)-N-methylaminoethanol (19.2g) in dry pyridine (100 ml) at room temperature. The mixture was stirred at room temperature for 3 hours, added to water (500 ml) and extracted with dichloromethane (3x250 ml). The combined extracts were washed with 2M hydrochloric acid (3x250 ml), saturated sodium bicarbonate solution (250 ml) and brine (250 ml), dried (MgSO₄), filtered and evaporated. The title compound was obtained pure following crystallisation from ethanol (m.p. 119-121°C).

¹H NMR δ (DMSO-d₆)

2.25 (3H, s); 3.05 (3H, s); 3.75 (2H, t); 4.35 (2H, t); 7.0 - 7.4 (6H, complex); 7.70 (2H, d).

Reference Preparation 242-(N-(2-Benzoxazolyl)-N-methylamino)ethanol methanesulphonyl ester

[0117]



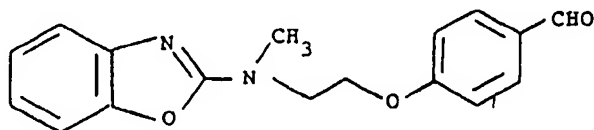
[0118] The title compound (m.p. 97-8°C) was prepared from N-(2-benzoxazolyl)-N-methylaminoethanol (19.2g) and methanesulphonyl chloride (11.5g) by a similar procedure to that used in Reference Preparation 23.

¹H NMR δ (CDCl₃)

2.90 (3H, s); 3.25 (3H, s); 3.7 (2H, t); 4.5 (2H, t); 6.90 - 7.4 (4H, complex).

Reference Preparation 254-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

[0119]



[0120] To a solution of 4-hydroxybenzaldehyde (7.32g) in dry dimethylformamide (100ml) was added portionwise sodium hydride (60%, 2.4g) with stirring at room temperature under nitrogen. When gas evolution ceased a solution

of 2-(N-methyl-N-(2-benzoxazolyl)amino)ethanol 4-toluenesulphonyl ester (17.3g) in dry dimethylformamide was added dropwise. The mixture was heated to 80°C and stirred at this temperature overnight. After cooling, the solution was poured into iced water (1 litre), extracted with ethyl acetate (3x500ml), and the combined extracts were washed with sodium hydroxide solution (2M; 500ml) and brine (500ml), dried (MgSO₄), filtered and evaporated. The title compound

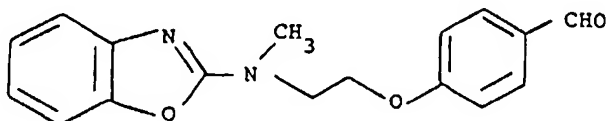
¹H NMR δ (DMSO-d₆)

3.25 (3H, s); 3.95 (2H, t); 4.40 (2H, t); 6.90-7.40 (6H, complex); 7.85 (2H, d); 9.90 (1H, s).

Reference Preparation 26

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

[0121]

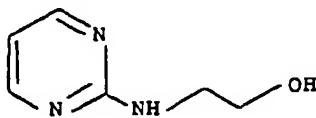


[0122] The title compound was prepared from 4-hydroxy benzaldehyde (1.22g) and 2-(N-methyl-N-(2-benzoxazolyl)-amino)ethanol methanesulphonyl ester (2.7g) in a similar manner to that described in Reference Preparation 25.

Reference Preparation 27

2-(2-Pyrimidinylamino)ethanol

[0123]



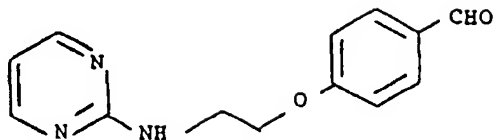
[0124] 2-Chloropyrimidine (5g) and ethanolamine (15ml) were stirred for 2 hours at 140°C. After cooling, the mixture was added to water (200ml) and continuously extracted with ethyl acetate (500ml) for 16 hours. The organic extract was dried (MgSO₄), filtered and evaporated to dryness. The title compound was obtained as a solid (m.p. 66°C), following chromatography on silica-gel in 3% methanol in dichloromethane.

¹H NMR δ (CDCl₃)

3.55 (2H, complex); 3.8 (2H, t); 4.3 (1H, broad s, exchanges with D₂O); 6.1 (1H, broad s, exchanges with D₂O); 6.55 (1H, t); 8.3 (2H, d).

Reference Preparation 284-[2-(2-Pyrimidinylamino)ethoxy]benzaldehyde

[0125]



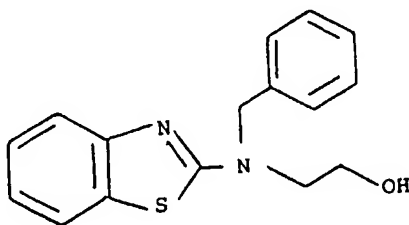
[0126] Sodium hydride (1.2g; 60% dispersion in oil) was added portionwise to a stirred solution of 2-(2-pyrimidinyl amino)ethanol (4g) in DMF (140ml) under an atmosphere of nitrogen. After the vigorous reaction had subsided 4-fluorobenzaldehyde (5.35g) was added and the solution heated to 80°C for 20 hours. After cooling the mixture was added to water (500ml) and extracted with diethyl ether (3x300ml). The organic extracts were washed with brine (2x200ml), dried (MgSO₄), filtered and evaporated to dryness. Chromatography of the residue on silica gel in 2% methanol in dichloromethane afforded the title compound, which was used in the next stage without further purification.

¹H NMR δ (CDCl₃)

3.8 (2H, complex); 4.2 (2H, t); 5.7 (1H, broad s, exchanges with D₂O); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

Reference Preparation 292-(N-(2-Benzothiazolyl)-N-benzylamino)ethanol

[0127]



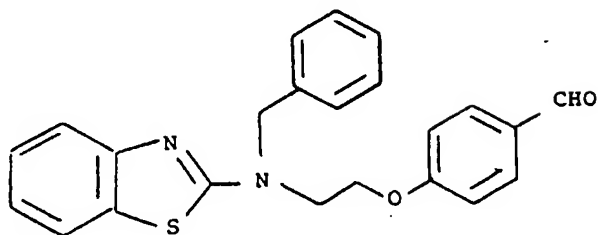
[0128] 2-Chlorobenzothiazole (13g) and 2-(benzylamino)ethanol (29g) were heated together in a sealed vessel at 120°C for 20h.. After cooling, the reaction mixture was dissolved in ethyl acetate (200ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate (3x100ml), water (3x100ml) and brine (100ml), dried over anhydrous magnesium sulphate and evaporated to give the title compound (m.p. 95-96°C; dichloromethane/hexane).

¹H NMR δ (CDCl₃)

3.8 (4H, m); 4.5 (1H, broad s, exchanges with D₂O); 4.7 (2H, s); 6.9-7.7 (9H, complex).

Reference Preparation 304-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzaldehyde

[0129]



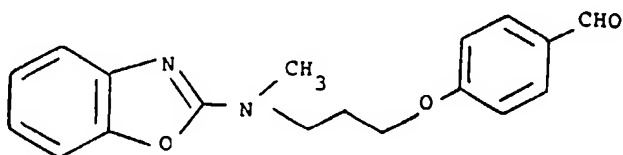
[0130] The title compound was prepared from 2-(N-(2-benzothiazolyl)-N-benzylamino)ethanol (8.25g) and 4-fluorobenzaldehyde (3.6g) by an analogous procedure to that described in Reference Preparation 22.

¹H NMR δ (CDCl₃)

4.0 (2h, t); 4.4 (2H, t); 4.9 (2H, s); 6.9-8.0 (13H, complex); 10.0 (1H, s).

Reference Preparation 314-[3-(N-Methyl-N-(2-benzoxazolyl)-amino)propoxy]benzaldehyde

[0131]



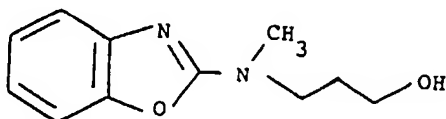
[0132] The title compound was prepared from 3-[(N-(2-benzoxazolyl)-N-methyl)amino]propan-1-ol (7.5g) and 4-fluorobenzaldehyde (6.78g) by a similar procedure to that described in Reference Preparation 22.

¹H NMR δ (CDCl₃)

2.0-2.4 (2H, complex); 3.2 (3H, s); 3.75 (2H, t); 4.2 (2H, t); 6.8-7.5 (6H, complex); 7.8 (2H, d); 9.9 (1H, s).

Reference Preparation 323-[(N-(2-Benzoxazolyl)-N-methyl)amino]propan-1-ol

[0133]



[0134] 2-Chlorobenzoxazole (15.36g) in dry tetrahydrofuran (50ml) was added dropwise to a mixture of 3-N-methylaminopropan-1-ol (9.8g) and triethylamine (20.2g) in dry tetrahydrofuran (130ml) with stirring, at room temperature.

After stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in dichloromethane (150ml), washed with water (3x100ml), brine (150ml), dried (MgSO₄), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2.5-3% methanol in dichloromethane.

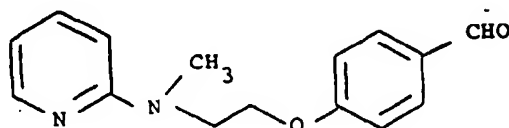
¹H NMR δ (CDCl₃)

1.8-2.1 (2H, complex); 3.2 (3H, s); 3.5-3.85 (4H, complex); 4.3 (1H, broad s, exchanges with D₂O); 6.8-7.5 (4H, complex).

Preparation 1

4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde

[0135]



[0136] The title compound was prepared from 2-(N-methyl-N-(2-pyridyl)amino)ethanol (8.9g) and 4-fluorobenzaldehyde by a similar procedure to that described in Reference Preparation 22.

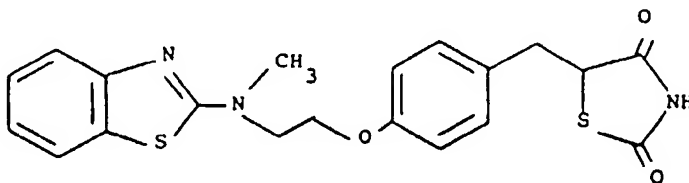
¹H NMR δ (CDCl₃)

3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.4 (2H, t); 6.9 (2H, d); 7.3 (1H, complex); 7.75 (2H, d); 8.15 (1H, d); 9.9 (1H, s).

Reference Example 1

5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

[0137]



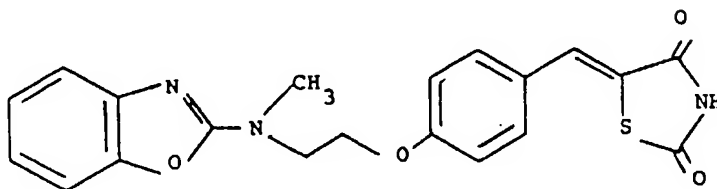
[0138] 5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy] benzylidene)-2,4-thiazolidinedione (2g) in dry 1,4-dioxan (70ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (3g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (m.p. 167-8°C) was obtained after crystallisation from methanol.

¹H NMR δ (DMSO-d₆)

2.9-3.4 (2H, complex); 3.25 (3H, s); 3.9 (2H, complex); 4.25 (2H, complex); 4.8 (1H, s); 6.8-7.75 (8H, complex); 12.0 (1H, s, exchanges with D₂O).

Reference Example 25-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

[0139]



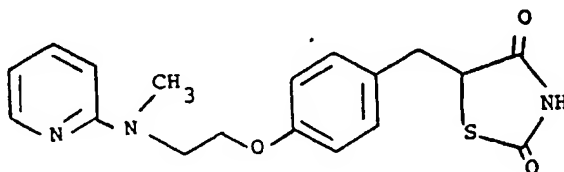
[0140] A solution of 4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde (1.6g) and 2,4-thiazolidinedione (0.63g) in toluene (100ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 227 - 9°C).

¹H NMR δ (DMSO-d₆)

3.20 (3H, s); 3.90 (2H, t); 4.30 (2H, t); 6.9 - 7.75 (10H, complex).

EXAMPLE 15-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

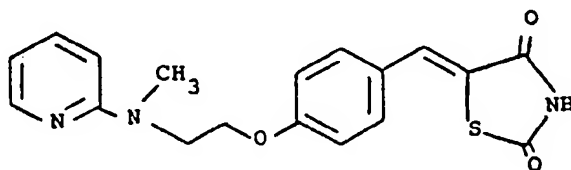
[0141]



[0142] The title compound (m.p. 153-5°C; MeOH) was obtained from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Reference Example 1.

¹H NMR δ (DMSO - d₆)2.9-3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5-6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D₂O).Reference EXAMPLE 35-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

[0143]



[0144] The title compound (m.p. 177-9°C) was obtained from 4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde (3.2g) and 2,4-thiazolidinedione (1.1g) by a similar procedure to that described in Reference Example 2.

¹H NMR δ (DMSO-D₂O)

3.1 (3H, s); 3.9 (2H, t); 4.2 (2H, t); 6.4-7.5 (7H, complex); 7.7 (1H, s); 8.1 (1H, d)

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test.

[0145] C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results expressed as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

Toxicology

[0146] No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

Claims

1. A compound 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.
2. A pharmaceutical composition comprising a compound according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.
3. A compound according to claim 1, for use as an active therapeutic substance.
4. A compound according to claim 3, for use in the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia or hypertension.
5. The use of a compound according to claim 1, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia or hypertension.

Patentansprüche

1. Eine Verbindung 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidindion oder eine tautomere Form davon und/oder ein pharmazeutisch verträgliches Salz davon, und/oder ein pharmazeutisch verträgliches Solvat davon.
2. Arzneimittel, umfassend eine Verbindung nach Anspruch 1, oder eine tautomere Form davon und /oder ein pharmazeutisch verträgliches Salz davon und/oder ein pharmazeutisch verträgliches Solvat davon, und einen pharmazeutisch verträglichen Träger dafür.
3. Verbindung nach Anspruch 1 zur Verwendung als eine wirksame therapeutische Substanz.
4. Verbindung nach Anspruch 3 zur Verwendung bei der Behandlung und/oder Prophylaxe von Hyperglykämie, Hyperlipidämie oder Hypertension.
5. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels für die Behandlung und/oder Prophylaxe von Hyperglykämie, Hyperlipidämie oder Hypertension.

Revendications

1. Composé consistant en 5-(4-[2-(N-méthyl-N-(2-pyridyl)amino)éthoxy]benzyl)-2,4-thiazolidinedione ou une de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables et/ou un de ses produits de solvation pharmaceutiquement acceptables.
2. Composition pharmaceutique comprenant un composé suivant la revendication 1 ou une de ses formes tautomères et/ou un de ses sels pharmaceutiquement acceptables et/ou un de ses produits de solvation pharmaceutiquement acceptables et un support pharmaceutiquement acceptable.
3. Composé suivant la revendication 1, destiné à être utilisé comme substance thérapeutique active.
4. Composé suivant la revendication 3, destiné à être utilisé dans le traitement et/ou la prophylaxie de l'hyperglycémie, de l'hyperlipidémie ou de l'hypertension.
5. Utilisation d'un composé suivant la revendication 1 pour la production d'un médicament destiné au traitement et/ou à la prophylaxie de l'hyperglycémie, de l'hyperlipidémie ou de l'hypertension.